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Dated 27 April 2004

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31MAR03 E796488-8 D00239
P01/7700 0.00-0307370.7

1/77

THE PATENT OFFICE
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29 MAR 2003
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference PC/JM/P12190GB

2. Patent application number
(The Patent Office will fill in this part) 29 MAR 2003 0307370.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

MITSUBISHI PHARMA CORPORATION
2-2-6, Nihonbashi-Honcho
Chuo-ku
Tokyo 103-8405
JAPAN

08438616002
Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention Compounds I

5. Name of your agent *(If you have one)* CRUIKSHANK & FAIRWEATHER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

19 Royal Exchange Square
Glasgow G1 3AE
UNITED KINGDOM

Patents ADP number *(if you know it)* 547002 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	44
Claim(s)	4
Abstract	–
Drawing(s)	1 +1

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Cruikshank & Fairweather Date 28/3/03

CRUIKSHANK & FAIRWEATHER 28TH MARCH 2003

12. Name and daytime telephone number of person to contact in the United Kingdom DR. P. CHAPMAN - 0141-221-5767

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Notes

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COMPOUNDS I

Technical Field

This invention relates to novel amidine compounds for treating schizophrenia. The present invention also relates to a method of manufacturing such compounds, pharmaceutical formulations comprising said compounds, as well as medical uses and methods of treatment using said compounds.

Background Art

The antipsychotic drugs (APDs) currently used in the treatment of schizophrenia are less than optimal in many respects, showing a lack of efficacy against some of the symptoms of schizophrenia and a significant tendency to produce unpleasant side-effects. While all APDs are effective against the positive symptoms of schizophrenia in the majority of patients, they are all less than completely effective against the negative symptoms and cognitive deficits of the disease, with many APDs showing virtually no efficacy against these symptoms. Negative symptoms include loss of emotional responsiveness, lack of motivation and social withdrawal. Cognitive deficits include deficits in working memory, attention and executive function. In addition, in a significant proportion of patients, the positive symptoms which include hallucinations and delusions do not respond to conventional antipsychotic drugs. All current APDs share the common property of antagonist action at D2 dopamine receptors (Seeman, 2001). This is thought to underly their activity against the positive symptoms, but unfortunately is responsible also for unpleasant side-effects such as parkinsonian motor deficits and hyperprolactinaemia.

It is widely accepted that clozapine shows the most favourable therapeutic profile of current antipsychotic drugs used in the treatment of schizophrenia. While all APDs, including clozapine, are effective to some degree against the positive symptoms of schizophrenia, clozapine is more effective than other APDs against the negative symptoms and cognitive deficits of the disease, and is also effective in many patients who do not respond to conventional antipsychotic drugs. However, despite its high clinical efficacy, clozapine exhibits relatively low occupancy of D2 dopamine receptors. In common with most APDs, clozapine binds to many different neurotransmitter receptors implicated in psychosis.

Muscarinic m4 receptors (Eglen, 2001) are located in brain regions that have been implicated in psychosis, including the prefrontal cortex, and are present in the specific neurones which are compromised in the post-mortem prefrontal cortex tissue from schizophrenic patients. While most APDs either have no affinity for the m4 receptor or act as antagonists, there is some evidence that m4 agonists may show APD-like activity in some tests. This is consistent with evidence that the levels of m4 receptors may be reduced in prefrontal cortex from schizophrenic patients as compared to normal controls (Crook et al., 2001). In addition, serotonin 5HT7 receptors (Vanhoenacker et al., 2000) are strikingly localised to thalamic nuclei. Some of the more effective atypical APDs have significant 5HT7 affinity as part of their complex pharmacological profile.

We therefore hypothesised that the favourable therapeutic profile of clozapine might be based on its 5HT7 antagonist activity and muscarinic m4 agonist activity with low occupancy of D2 dopamine receptors. According to this hypothesis, an agent possessing 5HT7

antagonist activity and substantial muscarinic m4 agonist activity, yet without significant D2 dopamine affinity, is postulated to show antipsychotic efficacy against both positive and negative symptoms. Such an agent may show an improved therapeutic profile relative to existing APDs, in terms of improved clinical efficacy and reduced side effect profile.

There is a need for effective APDs which are able to ameliorate both positive and negative symptoms and the cognitive deficits of schizophrenia and/or bipolar disorder without significant D2 affinity.

Therefore it is a first object of the present invention to obviate and/or mitigate the deficiencies associated with current anti-psychotic drug treatments.

It is a second object of the present invention to provide at least one novel amidine compound which possesses serotonin 5-HT7 receptor antagonist activity and/or muscarinic m4 receptor agonist activity.

It is a third object of the present invention to provide at least one compound according to the second aspect which additionally possesses relatively low or negligible dopaminergic D2 affinity.

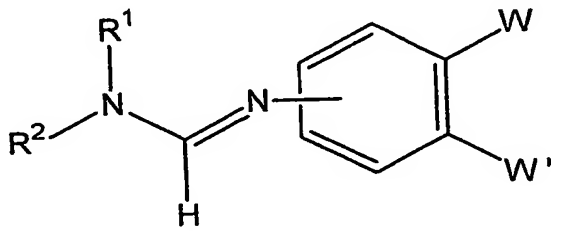
It is a fourth object of the present invention to provide a pharmaceutical composition comprising said compounds for the treatment of schizophrenia and/or bipolar disorder.

As used herein the term agonist refers to a ligand that, upon binding to said receptor, triggers activation of a chemical signalling cascade that results in a definable change in the behaviour or physical or biological state of a cell (including partial agonists which cause detectable but sub-maximal activation of signalling cascades) and the term antagonist refers to a molecule that, by virtue of binding to said receptor, is

able to block the cell-activating influence of an agonist to said receptor, and which itself does not result in substantial activation of the cell.

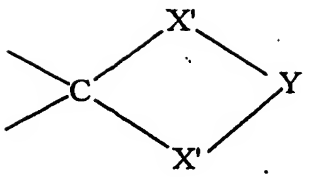
Summary of the Invention

According to a first aspect of the present invention there is provided a compound represented by formula (I):



(I)

wherein R^1 and R^2 independently are a hydrogen atom, a substituted or unsubstituted straight chain or branched chain C_{1-6} alkyl group or C_{1-6} alkoxy group, a substituted or unsubstituted C_{1-6} cycloalkyl group or a C_{1-6} cycloalkoxy group, or an aralkyl group, or R^1 and R^2 form, together with the nitrogen atom to which they are bonded, a cyclic amine; W and W' form, together with the benzene ring to which they are bonded, a fused five-membered, six-membered or seven-membered saturated carbocyclic ring being independently unsubstituted, substituted or fully substituted at each carbon atom of the ring by a group $-X-R^{13}$ wherein X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group or two of said $-X-R^{13}$ groups, together with the carbon atom in the ring to which they are both bonded, form a C=O group, a C=S group or the following group:



wherein both of X' are O or S and Y is a C_{1-3} alkylene group.

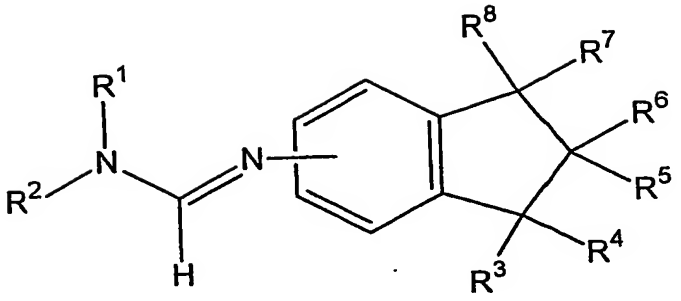
The cyclic amine may be substituted by a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group. Alternatively or additionally, the cyclic amine may be fused with a benzene ring. Said benzene ring may be substituted by one or two halogen atoms, C_{1-6} alkyl groups or C_{1-6} alkoxy groups.

The term "substituted" as used herein when in association with the saturated carbocyclic ring refers to one hydrogen atom of a carbon atom of the ring being replaced by a substituent, whereas the term "fully substituted" refers to both of the hydrogen atoms of a carbon atom of the ring being replaced by substituents.

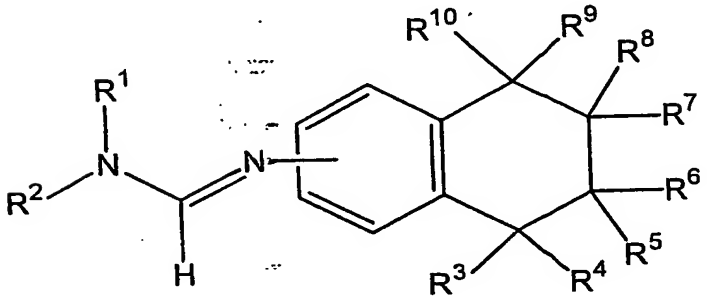
The present inventors hypothesised that exemplary compounds may contain the following features:

- a framework that contains an N^+ or a latent N^+
- a 5HT7 responsive group, which would typically be an aromatic system possibly with alkoxy substituents
- an M4 responsive group.

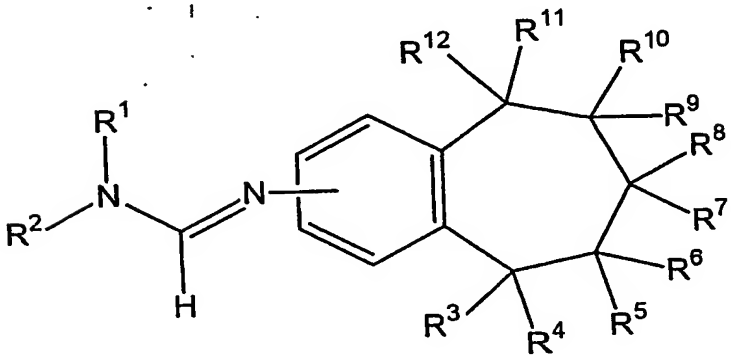
Further compounds of the present invention are represented by the following formulae (II), (III) and (IV) which fall within general formula (I):



(II)



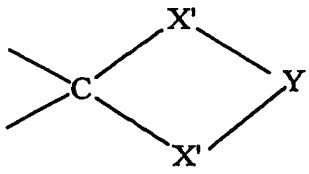
(III)



(IV)

In formulae (II), (III) and (IV), R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are independently a hydrogen atom or the group $-X-R^{13}$ wherein X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group.

Alternatively, R^3 and R^4, R^5 and R^6, R^7 and R^8, R^9 and R^{10}, and R^{11} and R^{12} together with the carbon atom in the ring to which they are both bonded, form a C=O group, a C=S group or the following group:



wherein both of X' are O or S and Y is a C_{1-3} alkylene group.

At each occurrence in formulae (I), (II), (III) and (IV) examples of C_{1-6} alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl and hexyl.

Examples of aralkyl groups are benzyl, phenylethyl, chlorobenzyl, methylbenzyl, and methoxybenzyl.

Examples of halogen atoms are chlorine, bromine, fluorine and iodine.

Examples of C_{1-6} alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentyloxy and hexyloxy.

An example of an acyl group is a C_{2-6} alkanoyl group for example an acetyl, propionyl, butyryl, pentanoyl or hexanoyl.

Examples of aroyl groups are benzoyl, phenylacetyl, chlorobenzoyl, methylbenzoyl, methoxybenzoyl, dichlorobenzoyl, dimethylbenzoyl or dimethoxybenzoyl.

Examples of C_{1-3} alkylene groups are methylene, ethylene, propylene or trimethylene.

Preferred compounds, although not exclusively, are those represented by the above formulae when R^1 and R^2 form together with the nitrogen atom to which they are bonded, a four-membered, five-membered or six-membered cylic amine.

The six-membered cyclic amine is preferably fused with a benzene ring, typically at carbon atoms 4a and 8a (according to isoquinoline numbering nomenclature).

The said benzene ring may also be substituted at any two adjacent carbon atoms.

Preferably said substitution is with a C_{1-6} alkoxy group which is preferably a methoxy group.

Alternatively, R^1 and R^2 may both be a C_{1-6} alkyl group.

Preferably the alkyl group is a methyl group.

In a further embodiment, R^1 may be an aralkyl group, preferably a benzyl group and R^2 may be a C_{1-6} alkyl group, preferably a methyl group.

The five-membered, six-membered or seven-membered saturated (except at the ring fusion) carbocyclic ring is typically substituted by a hydroxyl or an O-acyl group.

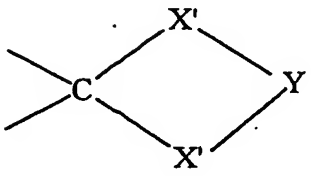
Preferably the acyl part of the O-acyl group is a C_{2-6} alkanoyl group such as an acetyl group or a propionyl group.

Typically the substitution is at carbon number 5 of the seven-membered benzocycloheptyl ring systems and carbon number 1 of the five-membered indanyl and six-membered tetrahydronaphthalenyl ring systems.

Alternatively, the five-membered, six-membered or seven-membered saturated carbocyclic ring may be substituted with an O-aroyl group in which the aroyl part is typically a benzoyl group. The benzene ring of the benzoyl group may be further substituted with halogen atoms such as chlorine atoms. Typically two chlorine atoms are present, preferably at positions 3 and 4 of the benzene ring.

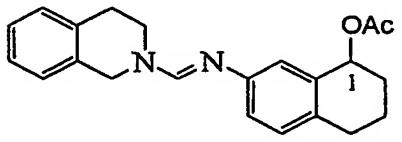
The carbocyclic ring may instead be substituted with a thiol group or a thio group such as a C_{1-6} alkyl thio group. A typical group is a butylthio group.

Alternatively the carbocyclic ring may be substituted by the group $-X-R^{13}$ when it forms the group:

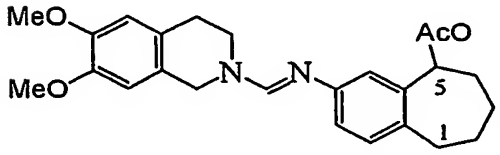


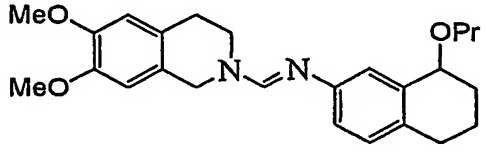
Preferably X^1 is S and Y is a C_2 alkylene group i.e. an ethylene group.

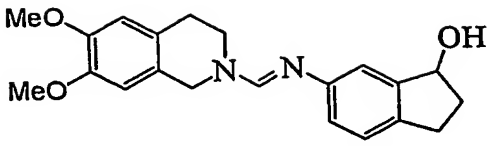
Examples of preferred compounds of the present invention are represented by the following formulae, some of which are named and ring positions numbered to indicate placement of substituents as used herein within the structural formulae.

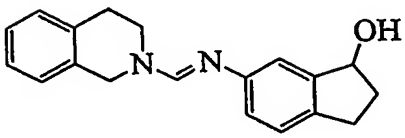


Acetic acid 7-[(3,4-dihydro-1*H*-isoquinolin-2-yl methylene)-amino]-1,2,3,4-tetrahydronaphthalen-1-yl ester

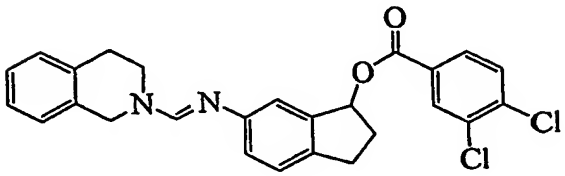


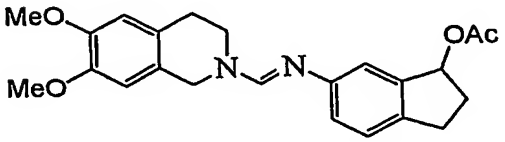


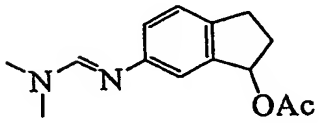


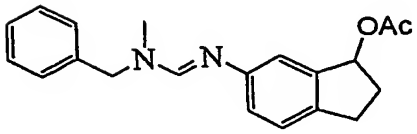


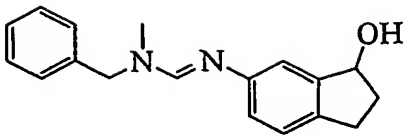
6-[(3,4-dihydro-1*H*-isoquinolin-2-ylmethylene)-amino]-indan-1-ol

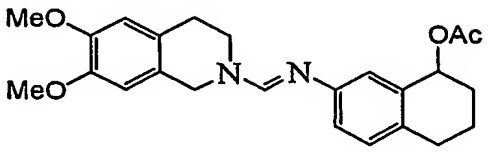


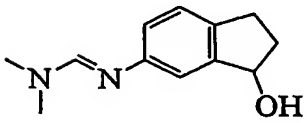


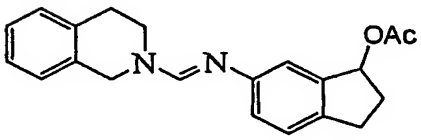




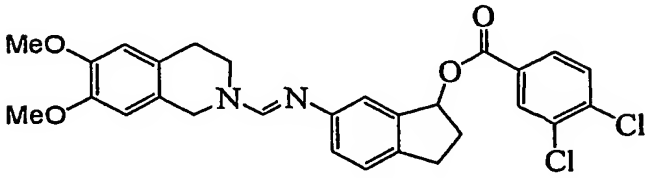


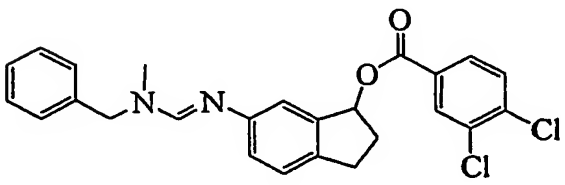


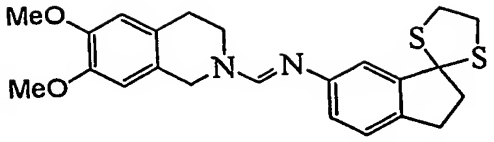


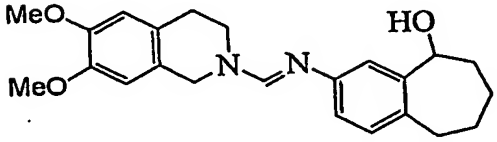


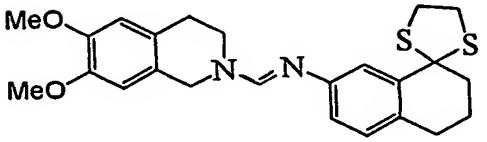
Acetic acid 6-[(3,4-dihydro-1*H*-isoquinolin-2-yl methylene)-amino]-indan-1-yl ester

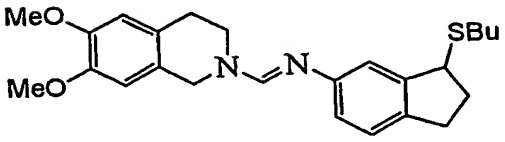












Preferably the said compounds according to any of the formulae (I), (II), (III) or (IV) possess serotonin 5-HT7 receptor antagonist activity and/or muscarinic m4 receptor agonist activity.

Preferably the compounds additionally have a low or substantially no dopaminergic D2 receptor affinity.

A low dopaminergic D2 receptor affinity may be, for example, a D2 receptor affinity having a minimum of at least 5 fold less than the affinity for the muscarinic m4 and/or serotonin 5-HT7 receptors.

More preferably the dopaminergic D2 receptor affinity is a D2 receptor affinity at least 50 fold less

than the affinity for the muscarinic m4 and/or serotonin 5-HT7 receptors.

For the avoidance of doubt the compounds of the present invention may be provided as pharmaceutically acceptable salts or derivatives.

It is understood that the present invention extends to each of the stereoisomers of the compounds of formulae (I), (II), (III) and (IV) as well as the racemates.

According to a second aspect of the present invention, the amidine compounds represented by formulae (I), (II), (III) and (IV) may be prepared by:

(i) providing an aromatic amine compound;

(ii) providing a formamide compound; and

(iii) coupling the aromatic amine with the formamide to give said amidine compound.

The formamide may be made by condensing an amine with an anhydride derived from formic acid.

The aromatic amine may be produced by reduction of an aromatic nitro compound, which can be prepared by nitration of an arene.

The compounds of formulae (I), (II), (III) and (IV) and their pharmaceutically acceptable salts can be prepared according to the following procedure for the coupling of amine and formamide, hydrolysis of ester and preparation of salt form of amidine:

(1) To a solution of formamide (2.0eq.) in dry dichloromethane (5mL/mmol of amine) under nitrogen at room temperature was added phosphorus oxychloride (2.0eq.) dropwise. The solution was stirred at room

temperature for 30min. The resulting solution was transferred to a flask containing amine (1.0eq) via a cannula under nitrogen and the reaction continued at room temperature for 2 to 3h. The mixture was diluted with dichloromethane and washed with sodium hydroxide solution (2M), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography with suitable eluent afforded the corresponding amidine (base form). Yields ranged from 40 to 60%.

(2) The hydrolysis of some of the coupling product (acetate esters) was performed by dissolving samples in methanol containing a catalytic amount of potassium carbonate at room temperature. The reaction was followed by TLC. The solvent was removed and the residue was dissolved in dichloromethane, washed with water, dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography gave alcohols.

(3) The salt form of the amidine was made by dissolving the amidine free base sample in dichloromethane and washing with, for example hydrochloric acid (2M), and drying over magnesium sulfate. Filtration and concentration afforded the corresponding salt form of amidine.

The compounds of the present invention may be provided as pharmaceutical formulations wherein the compound is admixed with a pharmaceutically acceptable carrier (e.g. binder, corrective, corrigent, disintegrator, emulsion, excipient), diluent or solibilizer to give a pharmaceutical composition by a conventional manner, which is formulated into, for example, tablet, capsule, granule, powder, syrup, suspension, solution, injection, infusion, deposit agent,

suppository and administered for example orally or parenterally.

When the tablets are used for oral administration, typically used carriers include sucrose, lactose, mannitol, maltitol, dextran, corn starch, typical lublicants such as magnesium stearate, preservatives such as paraben, sorbin, antioxidants such as ascorbic acid, α-tocopherol, cystein, disintegrators or binders. When administered orally as capsules, effective diluents include lactose and dry corn starch. A liquid for oral use includes syrup, suspension, solution and emulsion, which may contain a typical inert diluent used in this field, such as water. In addition, sweeteners or flavors may be contained.

In the case of parenteral administration such as subcutaneous injection, intraveneous injection, intramuscular injection, intraperitoneal injection or infusion, the pH of the active ingredient solution may be appropriately adequately adjusted, bufferized or sterilized. Examples of usable vehicle or solvent include distilled water, Ringer water and isotonic brine. For intraveneous use, the total concentration of solute is adjusted to make the solution isotonic.

Suppositories may be prepared by admixing the compounds of the present invention with a suitable nonirritative excipient such as those that are solid at normal temperature but become liquid at the temperature in the intestine and melt in rectum to release the active ingredient, such as cocoa butter and polyethylene glycols.

The dose can be determined depending on age, body weight, administration time, administration method, combination of drugs, the level of condition for which a patient is undergoing therapy, and other factors. While

the daily dose may vary depending on the conditions and body weight of patients, the species of active ingredient, and administration route, in the case of oral use, the daily dose is about 0.1-100 mg/person/day, preferably 0.5-30 mg/person/day. In the case of parenteral use, the daily dose is desirably 0.1-50 mg/person/day, preferably 0.1-30 mg/person/day for subsutaneous injection, intraveneous injection, intramuscular injection and intrarectal administration.

Accordingly the compounds of the present invention, represented by formulae (I), (II), (III) and (IV) may be used in a method for treating psychotic disorders, for example schizophrenia e.g. the positive and/or negative symptoms of schizophrenia, and/or the cognitive deficits of schizophrenia, and/or bipolar disorder.

The present invention accordingly provides the compounds represented by formulae (I), (II), (III) and (IV) for use in medicine or therapy.

According to a further aspect of the present invention, there is provided use of the compounds represented by formulae (I), (II), (III) and (IV) in the preparation of a medicament for use in the treatment of psychotic disorders, for example, schizophrenia e.g. the positive and/or negative symptoms of schizophrenia and/or the cognitive deficits of schizophrenia, and/or bipolar disorder.

The present invention will now be further described with reference to the figure and examples in which:

Figure 1 shows the modulation of PACAP-induced stimulation of cAMP by the compounds 25 and 32.

Example 1 shows the various methods and results of screening for binding affinity of the compounds of the present invention and in vivo testing;

Example 2 describes several examples for the preparation of the compounds of the present invention.

Example 1

The compounds of the present invention were screened for binding affinity using membranes containing stably expressed human M4 muscarinic receptors or human 5HT7 receptors.

M4 assay:

Total volume 200µl/well. Membrane concentration - human M4 membranes (NEN) - 8µg/ml; ^{3}H-NMS 0.25nM; Sample conc. 10nM-300µM; Atropine Displacement Curve - 0.3nM-1µM.

The plates are incubated at 20°C for 60 minutes in the dark to avoid any photo degradation. Membranes are harvested by rapid filtration using a vacuum manifold under 700mbar pressure. The plates are washed 3 times with 200ul per well of ice-cold wash buffer. Plates are dried at 40°C for 1 hour, 100µl scintillation fluid is added to each well and cpm determined using a Microbeta scintillation counter.

5HT7 assay:

Total volume 200µl/well. Membrane concentration - human $5HT_7$ membrane (purchased from Euroscreen) - 6µg/ml;^{3}H-5CT 0.5nM; Sample conc. 10nM-300µM; 8OH-DPAT Displacement Curve - 1nM-3µM. The plates are incubated at 20°C for 120 minutes in the dark to avoid any photo degradation. Membranes are harvested by rapid filtration using a vacuum manifold under 700mbar pressure. The plates are washed 3 times with 200ul/well of ice-cold

wash buffer. Plates are dried at 40°C for 1 hour (Higher CPMs are obtained when the filters are dried) 100µl scintillation fluid is added to each well and cpm determined using a Microbeta scintillation counter.

D2 assay:

Total volume 200µl/well. Membrane concentration - human D2 membrane (purchased from Euroscreen) - 10µg/ml; ^{3}H-spiperone 0.5nM; Sample conc. 10nM-300µM; Haloperidol Displacement Curve - 1nM-10µM. The plates are incubated at 25°C for 60 minutes in the dark to avoid any photo degradation.

Membranes are harvested by rapid filtration using a vacuum manifold under 700mbar pressure. The plates are washed 3 times with 200ul/well of ice-cold wash buffer. Plates are dried at 40°C for 1 hour (Higher CPMs are obtained when the filters are dried). 100µl scintillation fluid is added to each well and cpm determined using a Microbeta scintillation counter.

The following are examples showing data for Compounds 32 and 34

Compound	Ki (5HT7) (µM)	Ki (M4) (µM)	Ki (D2) (µM)
Compound 32	0.4	0.32	>300
Compound 34	2.7	2.8	>300

Efficacy (cAMP): Homogenate assay for c-AMP production

Methods:

N1E-115 cells were harvested by scraping and placed in Ribolyser tubes on dry ice. Ice cold buffer (0.5ml) containing 50mM Tris HCl, 0.4 mM EDTA and 0.4 mM EGTA (pH 7.4) was added to the tubes. The tubes were then placed in a Ribolyser and shaken at 4g for 20sec. The homogenate was then transferred to eppendorf tubes and was then centrifuged at 19,700g for 30 min at 4°C. The pellet was resuspended in ice cold 50mM Tris HCl (pH7.4) at a concentration of 50mg ml^{-1} wet weight of tissue. The homogenate was stored in aliquots at-70°C. Protein concentrations of the homogenates were determined using a Bio-Rad protein determination kit. The assay was carried out in a final assay volume of 120µl containing 50mM Tris HCl (pH7.4), 5 mM $MgCl_2$ 50 µM GTP, 200 µM ATP, 120 µM sucrose, 0.4 mM EDTA, 0.4 mM EGTA, 200 µM ascorbic acid, 20 µM papaverine, 200 µM rolipram, 10 µM vinpocetine, 10mM phosphocreatinine, 0.4mM DTT, 100nM WAY 100635, 1 µM propranolol, 36 µg bacitracin, 4.8U creatine phosphokinase, 3.6 KIU aprotinin. Homogenate ($1mgml^{-1}$) was preincubated with the test compound in ice cold assay buffer for 10 min. PACAP (0.1nM) was then added to the tubes. The tubes were then incubated at 30°C for 20 min and then at 99°C for 5 min. Levels of c-AMP in the tubes were measured using the Amersham Pharmacia Biotech Biotrak c-AMP enzymeimmunoassay kit

Results:

Mouse N1E-115 cells express a pure population of M4 muscarinic receptors, negatively coupled to camp levels. Known muscarinic agonists with activity at M4 receptors, including oxotremorine and acetylcholine, showed the ability to reduce cAMP levels .

Compounds of this series also showed similar agonist activity: an example is shown for 32 in Figure 1.

Compound 32 was able to reduce cAMP levels, and the effect was blocked by the muscarinic antagonist atropine.

In vivo activity:

To test the hypothesis that these compounds would show efficacy in the treatment of schizophrenia, we tested their inhibitory effect on a standard test for antipsychotic activity - amphetamine-induced hyperactivity in rats.

Methods

Male Long Evans rats (190-280 g) in each group of five were used.

Amphetamine was dissolved in saline, and test compounds were dissolved or suspended in 0.5 % hydroxypropylmethylcellulose (HPMC) solution. All the test compounds were injected intraperitoneally in a volume of 0.1 ml / 100 g, and control rats were treated with the respective vehicle.

The plastic open-field box (40x40x40(H) cm) was used to measure the locomotor activity of rats. The locomotor activity was expressed as the number of line crossings marked on the floor of the test box at 20 cm square. Individual rats were placed in the test box just after the injection of amphetamine, and were allowed to habituate there for 10 min. The line crossings were counted over 15 min thereafter. The behavioural observation was conducted on two rats simultaneously using two test boxes.

Test compounds were pretreated 30 min before the injection of amphetamine.

Results

32 suppressed the hyperactivity in a dose-dependent manner, of which ED50 value was estimated as 8.1 (95% confidence limits; 4.4-15) mg/kg,i.p. (Table 2).

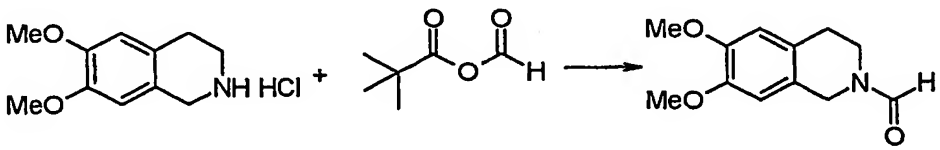
Table 2 Effect of 32 on amphetamine-induced hyperactivity in rats

Dose (mg/kg,i.p.)	Line Crossings (mean±S.E.)
0 (Control)	111.6 ± 6.4
1	98.8 ± 7.3
3	89.6 ± 13.3
10	45.6 ± 8.3**

The compounds of formula (I) of the present invention are useful as a novel type of the antipsychotic agents which are effective for both the positive and negative symptoms of schizophrenia, which causes less side effects of extrapyramidal motor disorder and the like and which causes less serious side effects such as agranulocytosis and the like.

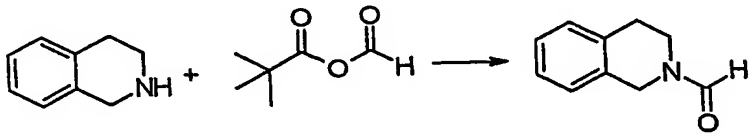
Example 2

The following are some examples for the preparation of the compounds of the present invention:



1

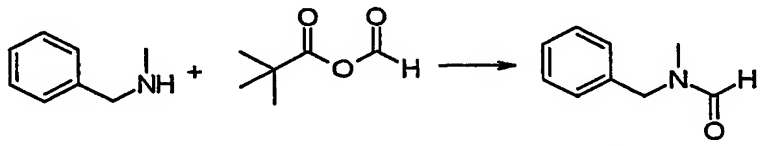
Trimethylacetic formic anhydride (5.3g, 40.77mmol) (E. J. Vlietstra *et al.*, *Journal of the Royal Netherlands Chemical Society*, 101/12, *1982*, 460-462) was added to a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (9.36g, 40.77mmol) in dry dichloromethane (40mL) cooled in an ice-water bath under nitrogen atmosphere, followed, dropwise, by dry triethylamine (4.95g, 58.924mmol). The mixture was stirred at room temperature for 1h and was then diluted with dichloromethane, washed with dilute hydrochloric acid (2M), saturated sodium bicarbonate, the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (pure EtOAc to dichloromethane/MeOH 95/5) afforded compound 1 (8.29g, 92%) as a white solid consisting of two rotamers (major:minor ratio ca. 2:1) in ^{1}HNMR spectrum (all *J* values are quoted in Hertz). ^{1}H NMR ($CDCl_3$, 400MHz): 2.78-2.85 (2H, m), 3.63 (major) and 3.78 (minor) [2H, 2 x t, *J* 5.9 (major) and 6.1 (minor)], 3.86 (6H, s), 4.48 (minor) and 4.61 (major) (2H, 2 x s), 6.58-6.63 (2H, m, ArH), 8.26 (minor) and 8.19 (major) (1H, 2 x s).



2

Trimethylacetic formic anhydride (3.12g, 23.79mmol) was added dropwise to a solution of 1,2,3,4-tetrahydroisoquinoline (2.9g, 21.79mmol) in chloroform (20mL) cooled in an ice-water bath under nitrogen atmosphere. The mixture was stirred at room temperature for 1h and then diluted with dichloromethane, washed with dilute hydrochloric acid (2M), saturated sodium

bicarbonate, the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (pure EtOAc to dichlormethane/MeOH 95/5) afforded compound 2 (2.98g, 85%) as a pale yellow oil, consisting of two isomers (major:minor ratio, *ca.* 1.5:1) in ^1H NMR spectrum ($CDCl_3$, 400MHz) ^1H NMR: 2.86-2.93(2H, m, $ArCH_2$), 3.65 (major) and 3.79 (minor) [2H, 2 x t, *J* 5.9 (major), 6.1 (minor) CH_2N], 4.54 (minor) and 4.69 (major) (2H, 2 x s, $ArCH_2N$), 7.09-7.23 (4H, m, ArH), 8.20 (major) and 8.25 (minor) (1H, s, CHO).



3

Trimethylacetic formic anhydride (3.55g, 27.27mmol) was added dropwise to a solution of *N*-methylbenzylamine (3.0g, 24.79mmol) in dry dichloromethane (20mL) cooled in an ice-water bath under nitrogen atmosphere. The mixture was stirred at room temperature for 1h and then diluted with dichloromethane, washed with dilute hydrochloric acid (2M), saturated sodium bicarbonate, the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (pure EtOAc to dichloromethane/MeOH, 95/5) afforded compound 3 (3.1g, 84%) as a pale yellow oil, consisting of two rotamers (major:minor ratio *ca.* 1.2/1) in ^1H NMR spectrum. ^{1}HNMR ($CDCl_3$, 400MHz): 2.84 (major) and 2.90 (minor) (3H, 2 x s, NMe), 4.45 (major) and 4.85 (minor) (2H, 2 x s, NCH_2), 7.25-7.45 (5H, m, ArH), 8.22 (minor) and 8.34 (major) (1H, 2 x s, CHO).

Preparation of compound 4

A solution of potassium nitrate (50.5g, 0.5mol) in H_2SO_4 (200mL) was added, via a dropping funnel, to a solution of 1-indanone (60g, 0.454mol) in concentrated sulfuric acid (500mL) cooled in an ice-water bath at a speed to maintain an internal temperature below 15°C. After stirring at 0°C for 1h, the reaction mixture was poured into crushed ice and stirred for 30 min. The solid was filtered, washed with water, and air-dried. Purification by flash chromatography (toluene/EtOAc, 95/5) gave compound 4 (43.5g, 54%) as a pale yellow solid. ^1H NMR ($CDCl_3$, 400MHz): 2.81-2.85 (2H, m, CH_2), 3.28 (2H, t, *J* 6.1, CH_2), 7.67 (1H, d, *J* 8.4, ArH), 8.45 (1H, d, *J* 8.4, ArH), 8.56 (1H, s, ArH).

4 5

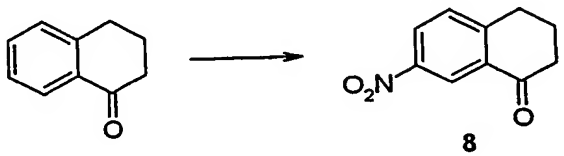
A solution of 4 (2.7g, 15.254mmol) in MeOH (50mL) was cooled in an ice-water bath and sodium borohydride (580mg, 15.254mmol) was added in three portions. The reaction was continued at room temperature for 30 min, quenched by adding hydrochloric acid (2M, 30mL). Most of the methanol was removed by rotavapor, the residue was diluted with water, extracted with dichloromethane, the organic phase was dried over $MgSO_4$, filtered and concentrated to provide crude alcohol 5 as a brown solid. The product was used in the next reaction without further purification. ^1H NMR ($CDCl_3$, 400MHz): 2.00-2.08 (1H, m, CH_2), 2.44 (1H, broad, OH), 2.56-2.63 (1H, m, CH_2), 2.85-2.94 (1H, m, CH_2), 3.08-3.16 (1H, m, CH_2), 5.30-5.31 (1H,

m, CHO), 7.36 (1H, d, *J* 8.3, ArH), 8.11 (1H, dd, *J* 8.3, 2.0, ArH), 8.22 (1H, d, *J* 2.0, ArH).

To the solution of crude 5 in pyridine (20mL) under nitrogen was added acetic anhydride (6mL) at 0°C and the mixture was stirred at room temperature overnight. The mixture was poured into water, extracted with diethyl ether, the organic phase was washed with hydrochloric acid (2M), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc, 75/25) gave compound 6 (3.23g, 95% for two steps) as a slightly yellow oil. ^1H NMR ($CDCl_3$, 400MHz): 2.10 (3H, s, Ac), 2.14-2.23 (1H, m, CH_2), 2.57-2.66 (1H, m, CH_2), 2.93-3.01 (1H, m, CH_2), 3.14-3.23 (1H, m, CH_2), 6.19-6.23(1H, m, CHO), 7.41 (1H, d, *J* 8.3Hz, ArH), 8.18 (1H, d, *J* 8.3Hz, ArH), 8.24 (1H, s, ArH).

A solution of 6 (1.0g, 4.52mmol) in MeOH (10mL) was subjected to hydrogenation at atmospheric pressure with Pd/C as catalyst. The reaction was followed carefully by TLC and was stopped when most of the starting material was consumed. The mixture was filtered through kieselguhr and was concentrated. Purification by flash chromatography (petroleum ether/EtOAc, 60/40) gave compound 7 (460mg, 53%) as a pale brown oil. ^1H NMR

($CDCl_3$, 400MHz): 2.01-2.11 (4H, m, Ac + CH_2), 2.41-2.51 (1H, m, CH_2), 2.72-2.79 (1H, m, CH_2), 2.95-3.03 (1H, m, CH_2), 3.71 (2H, broad, NH_2), 6.11-6.14 (1H, m, ArCH), 6.62 (1H, dd, *J* 8.4, 2.2, ArH), 5.75 (1H, d, *J* 2.2, ArH), 7.04 (1H, d, *J* 8.4, ArH).



8

Concentrated sulfuric acid (60 ml) was cooled to 0°C in an ice bath. α-Tetralone (8g, 54.7 mmol) was added with stirring, then potassium nitrate (6g, 59.3 mmol, 1.08 equiv.) dissolved in concentrated sulfuric acid (18 ml) was added dropwise via a dropping funnel, making sure that the temperature of the solution did not rise above 15°C. After addition, the solution was stirred for 1 h and then poured into crushed ice. The precipitate was filtered and washed with distilled water and then left to dry. Recrystallisation from a ethanol/water (1:1) yielded **8** as a slightly yellow solid (8.5 g, 81%), m.p. 104-106°C; I.R. (film)/cm^{-1} 1675, 1500, 1340; ^1H NMR (400 MHz, $CDCl_3$) 2.18-2.25 (2H, m, CH_2), 2.75 (2H, t, *J* 6.8, CH_2), 3.10 (2H, t, *J* 6.1, CH_2), 7.45 (1H, d, *J* 8.4, ArH), 8.30 (1H, dd, *J* 2.4, 8.4, ArH), 8.86 (1H, d, *J* 2.4, ArH).

8 **9**

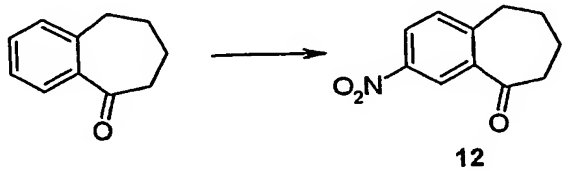
Sodium borohydride (6.95g, 183.9 mmol) was added to a solution of 3,4-dihydro-7-nitro-1(2*H*)-naphthalenone (8g, 41.8 mmol) in ethanol (240 ml) at 0°C. After the vigorous reaction subsided, the cooling bath was removed and the solution was then stirred for a further 10 min. Hydrochloric acid (2M) was then added and the crude reaction mixture was then extracted with ethyl acetate. Column chromatography on silica gel eluting with petroleum ether : ethyl acetate 4:1 gave alcohol **9** as a pale green solid (7.9 g, 98%), m.p. 107-109°C; I.R. (film)/cm^{-1} 3500; ^1H NMR (400 MHz, $CDCl_3$) 1.73-2.26 (4H, m, 2 x CH_2), 2.29 (1H, bs, OH), 2.78-2.91 (2H, m, CH_2), 4.78 (1H, m, CH), 7.17-7.26 (1H, d, *J* 8.4, ArH), 7.92-8.12 (1H, dd, *J* 2.4, 8.4, ArH), 8.30 (1H, d, *J* 2.4, ArH).

9 **10**

An excess of acetic anhydride (2.4 ml) was added to a solution of 7-nitro-1,2,3,4-tetrahydronaphthalen-1-ol **9** (0.45g, 2.33 mmol.) in pyridine (3.2 ml). The reaction mixture was stirred for 16 h at room temperature and then worked up to give the crude acetate **10**. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 5:1 gave pure acetate **10** as a slightly yellow oil (0.46g, 84%); ^1H NMR (400 MHz, $CDCl_3$) 1.84-2.10 (4H, m, 2 x CH_2), 2.13 (3H, s, CH_3), 2.80-3.00 (2H, m, CH_2), 6.00 (1H, t, *J* 4.8, CH), 7.28 (1H, d, *J* 8.4, ArH), 8.07 (1H, dd, *J* 2.4, 8.4, ArH), 8.16 (1H, d, *J* 2.4, ArH).

10 11

Copper (II) acetylacetonate (94 mg, 0.36 mmol) was dissolved in ethanol (70 ml) and sodium borohydride (68 mg, 1.79 mmol) was added under nitrogen. The reaction mixture was further stirred for 1 h at which time a black precipitate was formed. At this time ethanol (74 ml) and acetate **10** (0.42 g, 1.79 mmol) were added followed by sodium borohydride (135 mg, 3.58 mmol). The reaction was stirred for a further 2h. Then water was added and the solvent was removed *in vacuo*. After this, the mixture was diluted with diethyl ether and washed with brine, the ether layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 2:1 gave amine **11** as a yellow oil (0.36g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.74-1.97 (4H, m, 2 x CH_2), 2.09 (3H, s, CH_3), 2.59-2.78 (2H, m, CH_2), 3.57 (2H, bs, NH_2), 5.91 (1H, t, *J* 4.4, CH), 6.60 (2H, m, ArH), 6.93 (1H, d, *J* 7.7, ArH).



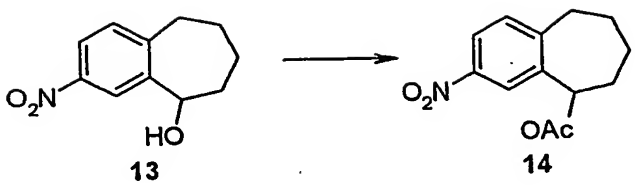
12

Concentrated sulfuric acid (55 ml) was cooled to 0°C in an ice bath. 1-Benzosuberone (8 g, 49.9 mmol) was added with stirring, then potassium nitrate (5.55g, 54.9 mmol) dissolved in concentrated sulfuric acid (15 ml) was added dropwise via a dropping funnel, making sure that

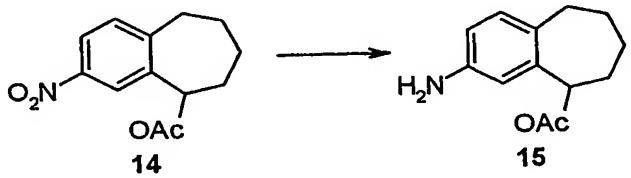
the temperature of the solution did not rise above 15°C. After addition, the solution was stirred for 1 h and then poured into crushed ice. The precipitate was filtered and washed with distilled water and then left to dry. Recrystallisation from ethanol/water 1:1 yielded nitro derivative **12** as a pale yellow solid (7.98 g, 78%), m.p. 91-93°C (lit. m.p. 92-93°C); ^{13}C NMR (100.61 MHz, $CDCl_3$) 25.1 (t), 31.5 (t), 32.1 (t), 38.9 (t), 123.6 (d), 127.9 (d), 129.1 (d), 138.2 (s), 145.6 (s), 146.1 (s), 197.6 (s).

12 **13**

Sodium borohydride (4.9g, 130.2 mmol) was added to a solution of nitroderivative **12** (6.1g, 29.6 mmol) in ethanol (160 ml) at 0°C. After the vigorous reaction subsided, the cooling bath was removed and the solution was then stirred for a further 10 min. Hydrochloric acid (2M) was then added and the crude reaction mixture was then extracted with ethyl acetate. Column chromatography on silica gel eluting with petroleum ether : ethyl acetate 5:1 gave alcohol **13** as a pale yellow solid (6.0 g, 98%), m.p. 115-117°C; ^1H NMR (400 MHz, $CDCl_3$) 1.61-1.93 (3H, m, CH_2), 2.05-2.13 (3H, m, CH_2), 2.78 (1H, m, CH_2), 3.04 (1H, m, CH_2), 5.02 (1H, m, CH), 7.25 (1H, d, *J* 8.8, ArH), 8.03 (1H, dd, *J* 2.3, 8.8, ArH), 8.42 (1H, d, *J* 2.3, ArH).

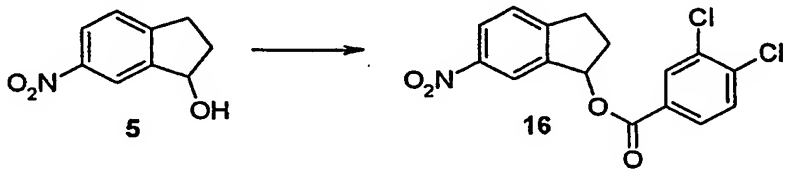


An excess of acetic anhydride (9 ml) was added to a solution of alcohol **13** (1.5g, 7.2 mmol) in pyridine (15 ml). The reaction mixture was stirred for 16 h at room temperature and then extracted, evaporated filtered and dried to give the crude acetate. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 6:1 gave pure the acetate **14** as a colourless oil (1.69g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.62-1.80 (2H, m, CH_2), 1.89-2.09 (4H, m, 2 x CH_2), 2.18 (3H, s, CH_3), 2.73 (1H, m, CH_2), 2.97 (1H, m, CH_2), 5.96 (1H, t, *J* 7.7, CH), 7.28 (1H, d, *J* 8.8, ArH), 8.09 (1H, dd, *J* 2.3, 8.8, ArH), 8.48 (1H, d, *J* 2.3, ArH).

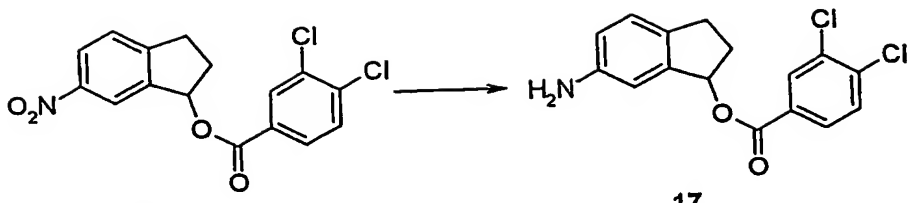


Copper (II)acetylacetonate (440 mg, 1.68 mmol) was dissolved in ethanol (300 ml) and sodium borohydride (319.3 mg, 8.4 mmol) was added under nitrogen. The reaction mixture was further stirred for 1h at which time a black precipitate had formed. Ethanol (350 ml) and acetate ester **14** (2.1 g, 8.4 mmol) were added, followed by sodium borohydride (638.7 mg, 16.8 mmol). The reaction was stirred for a further 2h. Then water was added and the solvent was removed *in vacuo*. After this, the residue was dissolved in diethyl ether and washed with brine, dried over anhydrous sodium sulfate, filtered and the

solvent was removed *in vacuo*. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 2:1 gave amine **15** as a yellow solid (1.77g, 96%), m.p. 84-86°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.52-1.65 (1H, m, CH_2), 1.68-1.79 (1H, m, CH_2), 1.80-1.99 (4H, m, 2 x CH_2), 2.15 (3H, s, CH_3), 2.62-2.69 (1H, m, CH_2), 2.82-2.88 (1H, m, CH_2), 5.84 (1H, t, *J* 7.7, CH), 6.49 (1H, dd, *J* 2.5, 7.9, ArH), 6.68 (1H, d, *J* 2.5, ArH), 6.90 (1H, d, *J* 7.9, ArH).



3,4-Dichlorobenzoyl chloride (3.1g, 14.8mmol) was added to a solution of crude **5** (2.4g, 13.4mmol) in pyridine (10mL) under nitrogen at 0°C, and the mixture was stirred at room temperature overnight before being poured into water, and then extracted with dichloromethane. The organic phase was washed with hydrochloric acid (2M), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (petroleum ether/ethyl acetate, 85/15) gave compound **16** (3.78g, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 400MHz): 2.31-2.39 (1H, m, CH_2), 2.70-2.79 (1H, m, CH_2), 3.02-3.10 (1H, m, CH_2), 3.24-3.33 (1H, m, CH_2), 6.45-6.48 (1H, m, CHO), 7.47 (1H, d, *J* 8.3, ArH), 7.53 (1H, d, *J* 8.3, ArH), 7.87 (1H, dd, *J*, 8.3, 2.0, ArH), 8.10 (1H, d, *J*, 2.0, ArH), 8.22 (1H, dd, *J*, 8.3, 2.0, ArH), 8.33 (1H, d, *J*, 2.0, ArH).



16 17

A solution of **16** (2.0g, 5.68mmol) in ethyl acetate (10mL) was subjected to hydrogenation at atmospheric pressure with Pd/C as catalyst. The reaction was followed carefully by TLC and was stopped when most of the starting material was consumed. The mixture was filtered through kieselguhr and was concentrated. Purification by flash chromatography (petroleum ether/ethyl acetate, 70/30) gave amine **17** (823mg, 45%) as a pale brown solid. ^{1}H NMR ($CDCl_3$, 400MHz): 2.17-2.25 (1H, m, CH_2), 2.55-2.64 (1H, m, CH_2), 2.81-2.92 (1H, m, CH_2), 2.05-3.12 (1H, m, CH_2), 3.66 (2H, broad, NH_2), 6.34-6.50 (1H, m, CHO), 6.69 (1H, dd, *J* 8.0, 2.0, ArH), 6.81 (1H, d, *J* 2.0, ArH), 7.10 (1H, d, *J* 8.0, ArH), 7.50 (1H, d, *J*, 8.4, ArH), 7.87 (1H, dd, *J*, 8.4, 1.9, ArH), 8.10 (1H, d, *J*, 1.9, ArH).

4 18

To a solution of **4** (2.40g, 13.56mmol) in dry DCM (20mL) under nitrogen atmosphere was added 1, 2-ethanedithiol (1.915g, 20.34mmol, 1.71mL) and $BF_3.OEt_2$ (1.92g, 13.56mmol, 1.67mL). The mixture was stirred at room temperature for 2 hours and was diluted with DCM (50mL) washed with aqueous NaOH (10%), dried over $MgSO_4$, filtered and concentrated to give **18** as a yellow oil (3.26g, 95%), which was used in next reaction without

purification. ^{1}H NMR ($CDCl_3$, 400MHz): 2.76 (2H, t, *J* 6.75, CH_2), 3.05 (2H, t, *J* 6.75, CH_2), 3.44-3.51 (2H, m, CH_2), 3.55-3.62 (2H, m, CH_2), 7.31 (1H, d, *J* 8.28, ArH), 8.08 (1H, dd, *J* 8.28, 2.19, ArH), 8.35 (1H, d, *J* 2.19, ArH).

18 **19**

A solution of **18** (500mg, 1.976mmol) and $SnCl_2.2H_2O$ (2.23g, 9.88mmol) in MeOH (15mL) was refluxed for 4 hours and then stirred at room temperature overnight. The mixture was quenched by adding saturated aqueous $NaHCO_3$ (30mL) carefully, extracted with ethyl acetate (50mL), the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc 75/25) gave compound **19** as a yellow oil (315mg, 71%). ^{1}H NMR ($CDCl_3$, 400MHz): 2.64 (2H, t, *J* 6.55, CH_2), 2.84 (2H, t, *J* 6.55, CH_2), 3.38-3.41 (2H, m, CH_2), 3.46-3.55 (2H, m, CH_2), 3.65 (2H, broad, NH_2), 6.54 (1H, dd, *J* 7.97, 2.07, ArH), 6.89 (1H, d, *J* 2.07, ArH), 6.95 (1H, d, *J* 7.97, ArH).

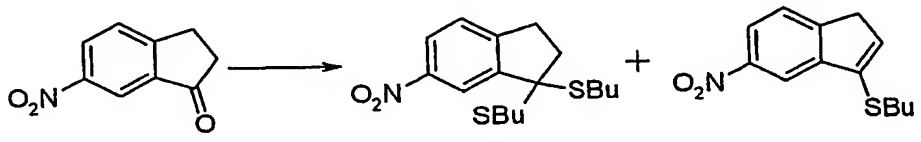
8 **20**

To a solution of **8** (1.0g, 5.235mmol) in dry DCM (10mL) was added 1,2-ethanedithiol (740mg, 7.853mmol, 0.66mL) and $BF_3.OEt_2$ (1.113g, 7.853mmol, 0.96mL) under nitrogen atmosphere. The mixture was stirred at room

temperature overnight, diluted with DCM (50mL), washed with 2N NaOH, dried over $MgSO_4$, filtered and concentrated. Compound 20 was obtained as slightly yellow solid (1.4g, 100%) and was used without purification in next reaction. ^1H NMR ($CDCl_3$, 400MHz): 2.02-2.08 (2H, m, CH_2), 2.40-2.43 (2H, m, CH_2), 2.87 (2H, t, *J* 6.38, CH_2), 3.47-3.54 (2H, m, CH_2), 3.62-3.70 (2H, m, CH_2), 7.14 (1H, d, *J* 8.49, ArH), 7.93 (1H, dd, *J* 8.49, 2.40, ArH), 8.80 (1H, d, *J* 2.40, ArH).

20 21

A suspension of 20 (1.4g, 5.235mmol) and $SnCl_2.2H_2O$ in MeOH (30mL) was refluxed under nitrogen atmosphere for 4 hours. The mixture was cooled to room temperature and poured into 100mL of saturated $NaHCO_3$, the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography afforded compound 21 as a slightly yellow oil (1.0g, 80%). ^1H NMR ($CDCl_3$, 400MHz): 1.62-2.00 (2H, m, CH_2), 2.30-2.39 (2H, m, CH_2), 2.70 (2H, t, *J* 6.41, CH_2), 3.30-3.34 (2H, m, CH_2), 3.38-3.61 (4H, m, CH_2 + NH_2), 6.51 (1H, dd, *J* 8.12, 2.28, ArH), 6.80 (1H, d, *J* 2.48, ArH), 7.29 (1H, d, *J* 8.12, ArH).

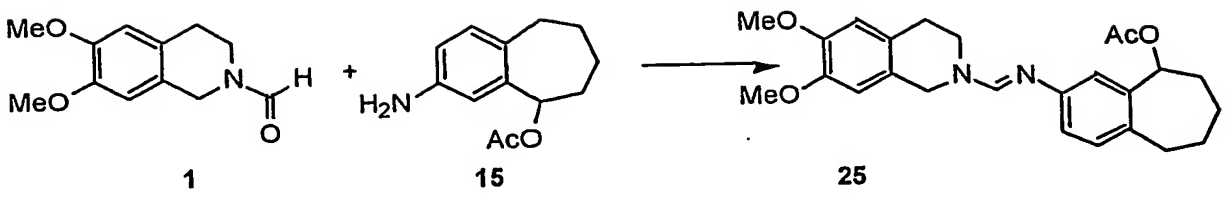


4 22 23

To a solution of **4** (1.0g, 5.65mmol) in chloroform (10mL) under nitrogen atmosphere at room temperature was added n-butanethiol (1.27g, 14.124mmol, 1.513mL) and chlorotrimethylsilane (1.534g, 14.124mmol, 1.805mL). The mixture was stirred at room temperature overnight and was diluted with DCM (20mL), washed with 2N NaOH, dried over $MgSO_4$, filtered and concentrated. Purification by column (petro-leum ether/ether 95/5) gave compound **22** (slightly yellow oil, 1.27g, 77%) and **23** (yellow solid, 290mg, 20%). ^{1}HNMR for **22**: ^{1}H NMR ($CDCl_3$, 400MHz): 0.89 (6H, t, *J* 7.28, CH_3). 1.32-1.43 (4H, m, CH_2), 1.45-1.61 (4H, m, CH_2), 2.46-2.53 (2H, m, CH_2), 2.59-2.67 (4H, m, CH_2), 3.10 (2H, t, *J* 6.92, CH_2), 7.38 (1H, d, *J* 8.06, ArH), 8.11-8.14 (2H, m, ArH). ^{1}HNMR for **23**: ^{1}H NMR ($CDCl_3$, 400MHz): 0.97 (3H, t, *J* 7.35, CH_3). 1.46-1.57 (2H, m, CH_2), 1.71-1.78 (2H, m, CH_2), 3.00 (2H, t, *J* 7.33, CH_2), 3.56 (2H, d, *J* 2.29, CH_2), 6.35 (1H, t, *J* 2.29, CH), 7.56 (1H, d, *J* 8.14, ArH), 8.14 (1H, dd, *J* 8.14, 2.11, ArH), 8.22 (1H, d, *J* 2.11, ArH).

23 **24**

A solution of **23** (40mg, 0.16mmol) in EtOAc (10mL) was subjected to hydrogenation at atmospheric pressure with Pd/C as catalyst overnight. After filtration, the solvent was removed to give a residue (20mg), that was used in the coupling reaction without further purification.

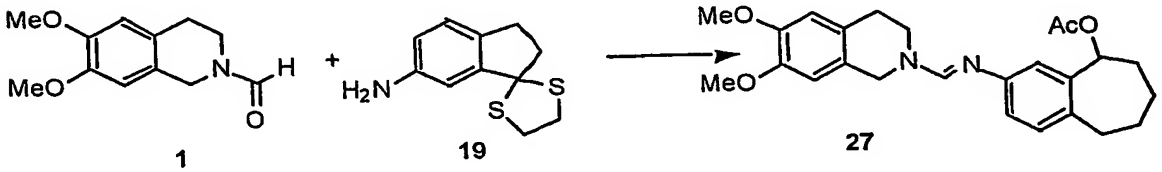


1 15 25

25 m.p. 160°C [decomp.]; (Found: MH^+ 423.2276, $C_{25}H_{30}N_2O_4$ requires *MH* 423.2284); *m/z* (EI) 423 ($[M+H]^+$, 5%), 362 (65), 192 (48), 177 (50), 115 (60), 44 (85), 43 (100).

25 26

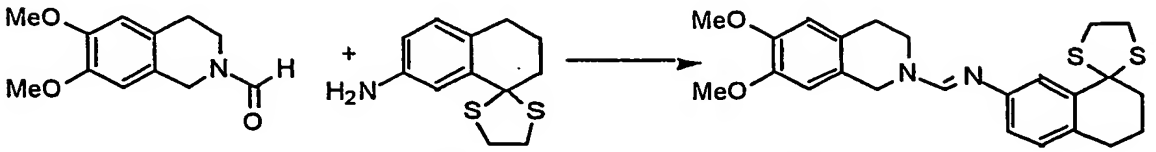
26 ^{1}H NMR ($CDCl_3$, 400MHz): 1.35-1.43 (1H, m, CH_2), 1.68-1.80 (3H, m, CH_2), 1.90-2.05 (2H, m, CH_2), 2.24 (1H, broad OH), 2.61-2.86 (4H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.85 (3H, s, CH_3), 3.86 (3H, s, CH_3), 4.63 (2H, broad, NCH_2), 4.85-4.88 (1H, m, OCH), 6.63 (1H, s, ArH), 6.64 (1H, s, ArH), 6.76 (1H, dd, *J* 7.81, 1.83 ArH), 6.97 (1H, d, *J* 7.81, ArH), 7.07 (1H, d, *J* 1.83, ArH), 7.70 (1H, s, N=CH). MS: $C_{23}H_{28}N_2O_3$, M+H, calculated 381.2178, found 381.2178



1 19 27

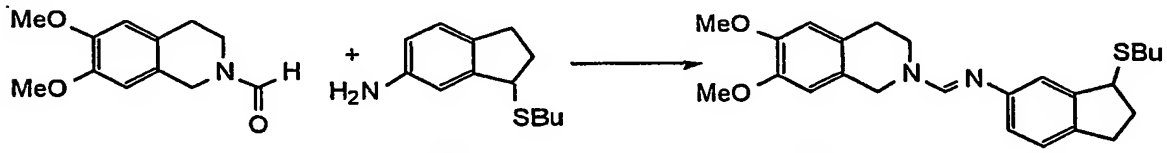
27 ^{1}H NMR ($CDCl_3$, 400MHz): 2.69 (2H, t, *J* 6.58, CH_2), 2.86 (2H, t, *J* 5.69, CH_2), 2.92 (2H, t, *J* 6.58, CH_2), 3.40-3.46 (2H, m, CH_2), 3.50-3.56 (2H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.86 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.66 (2H, broad, NCH_2), 6.64 (1H, s, ArH), 6.65 (1H, s, ArH),

6.87 (1H, dd, *J* 7.95, 1.89 ArH), 7.08 (1H, d, *J* 7.95, ArH), 7.17 (1H, d, *J* 1.89, ArH), 7.71 (1H, s, N=CH). MS: $C_{23}H_{26}N_2O_2S_2$, M+H, calculated 427.1514, found 427.1514



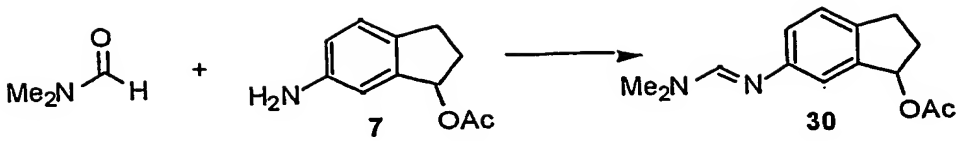
1 **21** **28**

28 ^{1}H NMR ($CDCl_3$, 400MHz): 2.69 (2H, t, *J* 6.58, CH_2), 1.97-2.02 (2H, m, CH_2), 2.37-2.40 (2H, m, CH_2), 2.76 (2H, t, *J* 5.91, CH_2), 2.85 (2H, t, *J* 5.66, CH_2), 3.40-3.48 (2H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.85 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.65 (2H, broad, NCH_2), 6.63 (1H, s, ArH), 6.64 (1H, s, ArH), 6.78 (1H, dd, *J* 8.09, 2.12 ArH), 6.90 (1H, d, *J* 8.09, ArH), 7.55 (1H, d, *J* 2.12, ArH), 7.67 (1H, s, N=CH). MS: $C_{24}H_{28}N_2O_2S_2$, M+H, calculated 441.1670, found 441.1662.

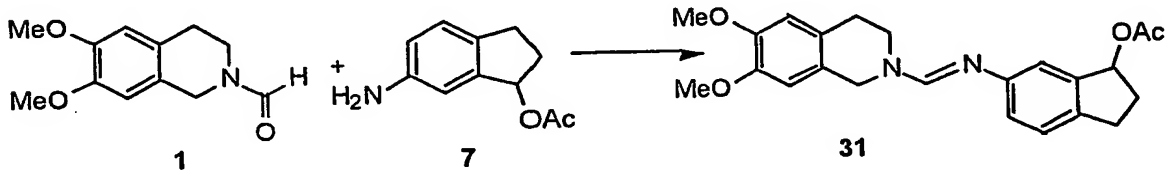


1 **24** **29**

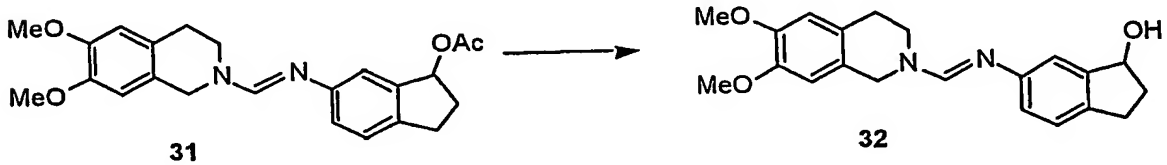
29 ^{1}H NMR ($CDCl_3$, 400MHz): 0.92 (3H, t, *J* 7.33, CH_3), 1.38-1.46 (2H, m, CH_2), 1.56-1.64 (2H, m, CH_2), 2.11-2.19 (1H, m, CH_2), 2.49-2.60 (3H, m, CH_2), 2.78-2.88 (3H, m, CH_2), 2.98-3.05 (1H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.86 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.29 (1H, dd, *J* 7.35, 5.35, SCH), 4.65 (2H, broad, NCH_2), 6.64 (1H, s, ArH), 6.65 (1H, s, ArH), 6.84 (1H, dd, *J* 7.92, 1.75 ArH), 6.97 (1H, d, *J* 1.75, ArH), 7.11 (1H, d, *J* 7.92, ArH), 7.69 (1H, s, N=CH).



30 ^{1}H NMR ($CDCl_3$, 400MHz): 2.03-2.14 (4H, m, Ac + CH_2), 2.44-2.53 (1H, m, CH_2), 2.76-2.87 (1H, m, CH_2), 2.94-3.07 (7H, m, NMe_2 + CH_2), 6.12-6.17 (1H, m, CHO), 6.90 (1H, dd, *J*, 7.9, 1.7Hz, ArH), 6.97 (1H, d, *J*, 1.7Hz, ArH). 7.13 (1H, 7.9Hz, ArH), 7.51 (1H, s, CH=N).



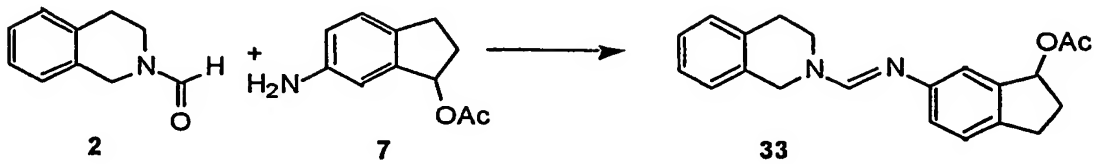
31 ^{1}H NMR ($CDCl_3$, 400MHz): 2.01-2.13 (4H, m, Ac + CH_2), 2.46-2.55 (1H, m, CH_2), 2.79-2.88 (3H, m, CH_2), 3.02-3.10 (1H, m, CH_2), 3.67 (2H, broad, CH_2), 3.86 (3H, s), 3.87 (3H, s), 4.66 (2H, broad, CH_2), 6.17-6.20 (1H, m, CHO), 6.64 (1H, s, ArH), 6.65 (1H, m, ArH), 6.95 (1H, d, *J*, 8.0Hz, ArH), 7.01 (1H, s, ArH), 7.16 (1H, d, *J*, 8.0Hz, ArH), 7.69 (1H, s, CH=N).



32 ^{1}H NMR ($CDCl_3$, 400MHz): 1.90-1.98 (1H, m), 2.17 (1H, broad), 2.44-2.52 (1H, m), 2.72-2.77 (1H, m), 2.84-2.87 (2H, m), 2.95-3.02 (1H, m), 3.70 (2H, broad), 3.85 (3H, s), 3.87 (3H, s), 4.65 (2H, broad), 5.19 (1H, t, *J*, 6.1, CHO), 6.63 (1H, s, ArH), 6.64 (1H, s, ArH), 6.90

(1H, d, *J*, 7.9, ArH), 7.02 (1H, s, ArH), 7.12 (1H, d, *J*, 7.9, ArH), 7.69 (1H, CH=N).

MS: $C_{21}H_{24}N_2O_3$, M+H, calculated 353.1865, found 353.1859



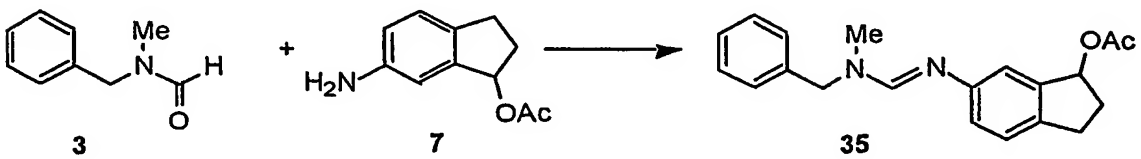
2 7 33

33 ^{1}H NMR $CDCl_3$, 400MHz): 2.15-2.23 (4H, m, Ac + CH_2), 2.55-2.64 (1H, m, CH_2), 2.88-2.96 (1H, m, CH_2), 3.01-3.02 (2H, m, CH_2), 3.10-3.19 (1H, m, CH_2), 3.79 (2H, broad, CH_2), 4.82 (2H, broad, CH_2), 6.26-6.29 (1H, m, CHO), 7.05 (1H, d, *J*, 7.9, ArH), 7.12 (1H, s, ArH), 7.25-7.35 (5H, m, ArH), 7.79 (1H, s, CH=N).

33 34

34 ^{1}H NMR ($CDCl_3$, 400MHz): 1.91-2.00 (1H, m), 2.44-2.52 (1H, m), 2.72-2.80 (2H, m), 2.93-3.03 (3H, m), 3.69 (2H, broad), 4.70 (2H, broad), 5.20 (1H, t, *J*, 6.2, CHO), 6.92 (1H, d, *J*, 7.9Hz, ArH), 7.05 (1H, m, ArH), 7.13-7.28 (5H, m, ArH), 7.70 (1H, s, CH=N).

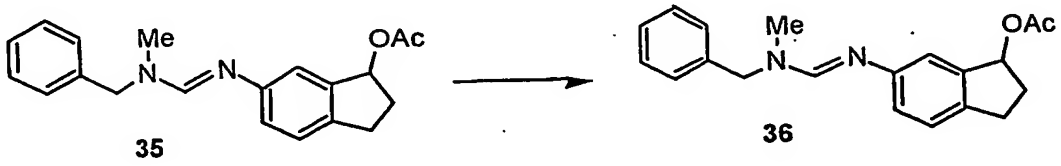
MS: $C_{19}H_{20}N_2O$, M+H, calculated 293.1654, found 293.1651



3 7 35

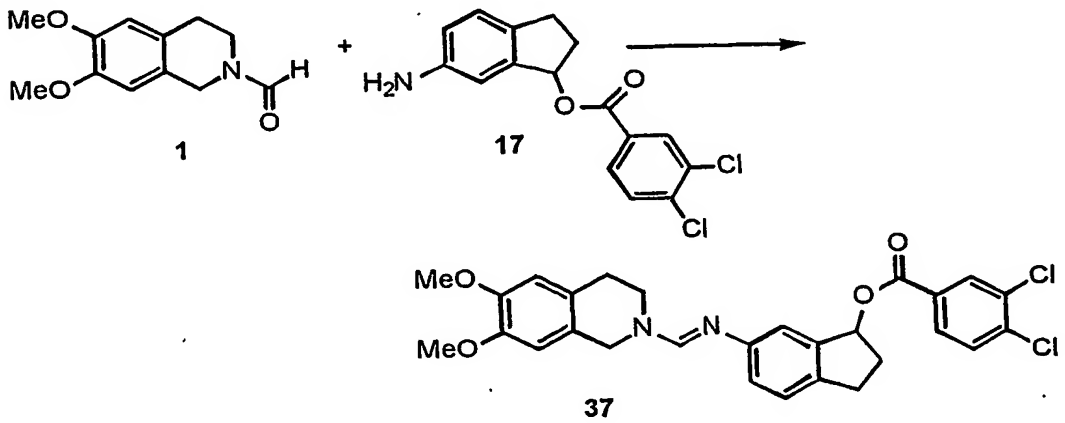
35 ^{1}H NMR ($CDCl_3$, 400MHz): 2.10-2.22 (4H, m, Ac + CH_2), 2.55-2.64 (1H, m, CH_2), 2.88-2.95 (1H, m, CH_2), 3.03

(3H, s, NMe), 3.11-3.18 (1H, m, CH_2), 4.50 (2H, broad, CH_2), 6.26-6.29 (1H, m, CHO), 7.06 (1H, d, *J*, 7.9, ArH), 7.14 (1H, s, ArH), 7.26 (1H, d, *J*, 7.9, ArH), 7.34-7.46 (5H, m, ArH), 7.83 (1H, broad, CH=N). MS: $C_{20}H_{22}N_2O_2$, M+H, calculated 323.1759, found 323.1765.



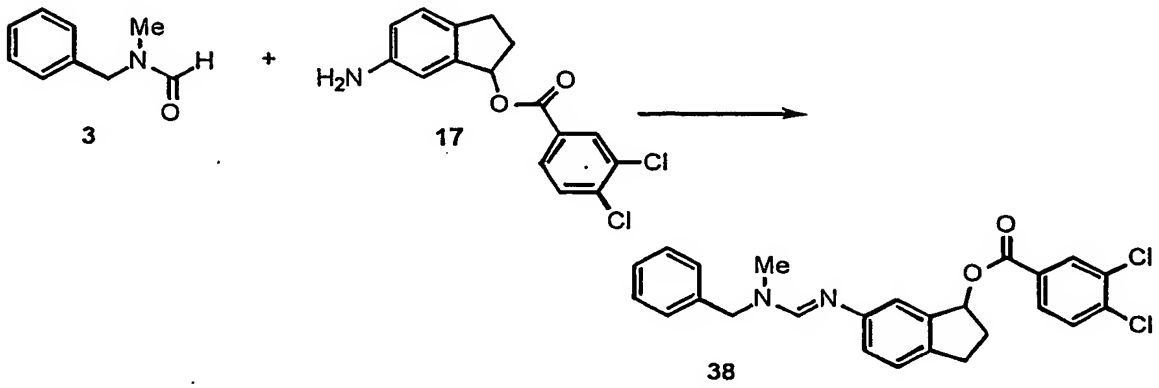
35 36

36 ^{1}H NMR ($CDCl_3$, 400MHz): 1.90-1.99 (1H, m, CH_2), 2.30 (1H, broad, OH), 2.44-2.53 (1H, m, CH_2), 2.72-2.80 (1H, m, CH_2), 2.95-3.11 (4H, m, NMe + CH_2), 4.50 (2H, broad, CH_2), 5.13-5.25 (1H, m, CHO), 6.92-6.94 (1H, m, ArH), 7.05 (1H, s, ArH), 7.13-7.16 (1H, m, ArH), 7.27-7.39 (5H, m, ArH), 7.76 (1H, broad, CH=N). MS: $C_{18}H_{20}N_2O$, M+H, calculated 281.1654, found 281.1648.

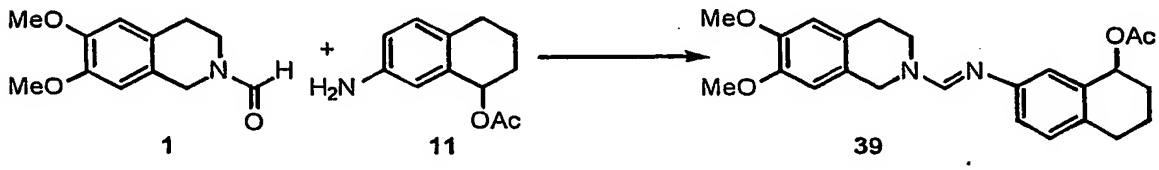


37 ^{1}H NMR ($CDCl_3$, 400MHz): 2.19-2.28 (1H, m, CH_2), 2.58-2.67 (1H, m, CH_2), 2.84-2.94 (3H, m, CH_2), 3.10-3.18 (1H, m, CH_2), 3.64 (2H, broad, CH_2), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 4.68 (2H, broad, CH_2), 6.40-6.43 (1H,

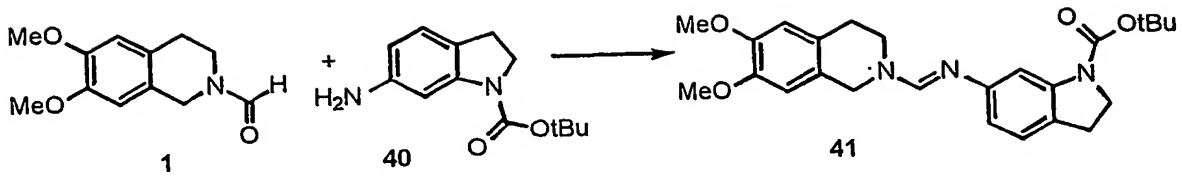
m, CHO), 6.62 (2H, s, ArH), 6.98 (1H, dd, *J*, 7.7, 1.6Hz, ArH), 7.08 (1H, d, *J*, 1.6, ArH), 7.19 (1H, d, *J*, 7.7, ArH), 7.48 (1H, d, *J*, 8.3, ArH), 7.69 (1H, s, CH=N), 7.86 (1H, dd, *J*, 8.3, 1.9Hz, ArH), 8.10 (1H, d, *J*, 1.9, ArH).



38 ^{1}H NMR ($CDCl_3$, 400MHz): 2.27-2.34 (1H, m, CH_2), 2.65-2.74 (1H, m, CH_2), 2.93-3.00 (4H, m, NMe + CH_2), 3.18-3.25 (1H, m, CH_2), 4.50 (2H, broad, CH_2), 6.48-6.51 (1H, m, CHO), 7.06 (1H, dd, *J*, 8.0, 1.8, ArH), 7.17 (1H, d, *J*, 1.8, ArH), 7.27-7.43 (6H, m, ArH), 7.54-7.56 (1H, m, ArH), 7.81 (1H, broad, CH=N), 7.93 (1H, dd, *J*, 8.4, 1.9, ArH), 8.18 (1H, d, *J*, 1.9, ArH).

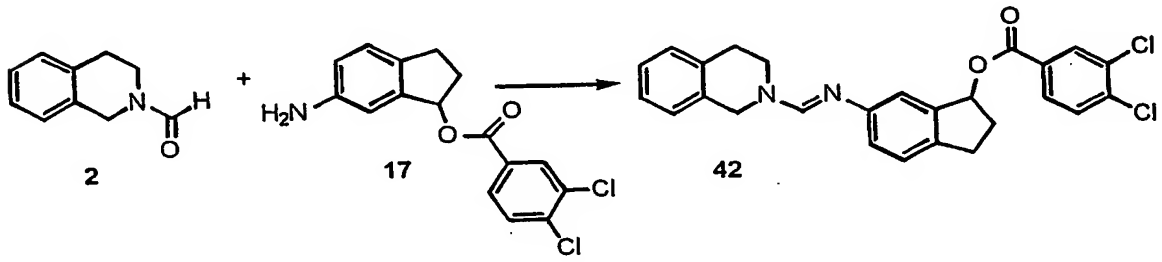


39 ^{1}H NMR ($CDCl_3$, 400MHz): 1.78-1.95 (4H, m, CH_2), 2.06 (3H, s, Ac), 2.65-2.85 (4H, m, CH_2), 3.61 (2H, broad, CH_2), 3.83-3.84 (6H, m, OMe), 4.66 (2H, broad, CH_2), 5.96 (1H, m, CHO), 6.61 (2H, s, ArH), 6.87-6.88 (2H, m, ArH), 7.00-7.03 (1H, m, ArH), 7.65 (1H, s, CH=N).



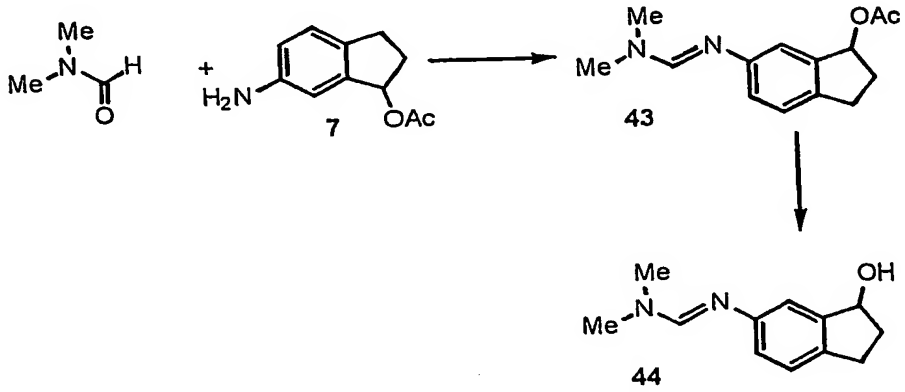
1 2 3

41 ^{1}HNMR (DMSO, 400MHz): 1.51 (9H, s, $C(CH_3)_3$), 2.92-3.08 (4H, m, $ArCH_2$), 3.75-3.76 (6H, m, OMe), 3.93-3.98 (4H, m, NCH_2), 4.86-4.90 (2H, m, $ArCH_2N$), 6.69 (1H, s, ArH), 6.81-6.89 (2H, m, ArH), 7.01-7.10 (1H, m, ArH), 7.25-7.28 (1H, m, ArH), 8.32 (1H, s, NCH=N), 8.82 (1H, broad, NH).



10

42 ^{1}HNMR ($CDCl_3$, 400MHz): 2.26-2.39 (2H, m, CH_2), 2.65-2.74 (1H, m, CH_2), 2.94-3.02 (2H, m, CH_2), 3.17-3.25 (1H, m, CH_2), 4.70 (2H, broad, CH_2N), 4.82 (2H, broad, $ArCH_2N$), 6.44-6.50 (1H, m, OCH), 7.04-7.05 (1H, m, ArH), 7.06-7.07 (1H, m, ArH), 7.14-7.38 (5H, m, ArH), 7.55-7.60 (1H, m, ArH), 7.76 (1H, s, NCH=N), 7.90-7.94 (1H, m, ArH), 8.15-8.17 (1H, m, ArH).



44 ^{1}HNMR ($CDCl_3$, 400MHz): 1.90-1.98 (1H, m, CH_2), 2.41-2.52 (1H, m, CH_2), 2.67-2.79 (1H, m, CH_2), 2.95-3.01 (7H, m, NCH_3 + CH_2), 5.19 (1H, t, *J* 6.05Hz), 6.86-6.88 (1H, m, ArH), 6.99-7.00 (1H, m, ArH), 7.11-7.13 (1H, m, ArH), 7.51-7.52 (1H, s, NCH=N). ^{13}CNMR ($CDCl_3$, 100MHz): 29.37 (CH_2), 36.34 (CH_2), 76.72 (CH), 116.44 (CH), 122.10 (CH), 125.39 (CH), 137.41 (C), 146.24 (C), 151.26 (C), 153.71 (CH).

References

Each of the following references is specifically incorporated herein by reference. In addition, one skilled in the art can rely on the contents of these references to make and use embodiments of this invention.

Cochran,S., McKerchar,C.M., Steward,L., Pratt,J.A. & Morris,B.J. (2002) Neuropsychopharmacology **28**, 265-275

Crook,J.M., Tomaskovic-Crook, E., Copolov,D.L. & Dean, B. (2001) Low muscarinic receptor binding in preforntal cortex from subjects with schizophrenia. Am.J.Psychiatry 158, 918-925

Eglen, (2001) Therapeutic opportunities from muscarinic receptor research. Trends in Pharmacological Sciences, 22:409-414

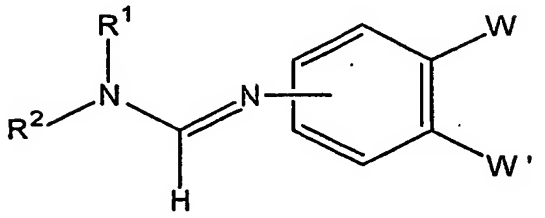
Luby, E.D.; Cohen, B.D.; Rosenbaum, G,; Gottlieb, J.S. and Kelley, R. (1959). Study of a new schizophrenomimetic drug. *Sernyl. Arch. Neurol. Psychiatry*, 81, 363-369.

Seeman P (2001) Antipsychotic drugs, dopamine receptors, and schizophrenia. Clinical Neuroscience Research 1, 53-60

Vanhoenacker, Guy Haegeman and Josée E. Leysen (2000) 5-HT7 receptors: current knowledge and future prospects. Trends in Pharmacological Sciences, 21,70-77.

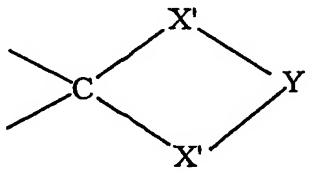
CLAIMS

1. A compound represented by formula (I):



(I)

where R^1 and R^2 independently are a hydrogen atom, a substituted or unsubstituted straight chain or branched chain C_{1-6} alkyl group or C_{1-6} alkoxy group, a substituted or unsubstituted C_{1-6} cycloalkyl group or a C_{1-6} cycloalkoxy group, or an aralkyl group, or R^1 and R^2 form, together with the nitrogen atom to which they are bonded, a cyclic amine; W and W' form, together with the benzene ring to which they are bonded, a fused five-membered, six-membered or seven-membered saturated carbocylic ring being independently unsubstituted, substituted or fully substituted at each carbon atom of the ring by a group - $X-R^{13}$ where X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group or two of said $-X-R^{13}$ groups, together with the carbon atom in the ring to which they are both bonded, form a C=O group, a C=S group or the following group:



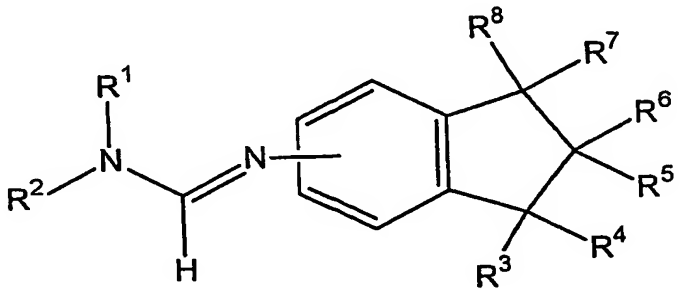
where both of X' are O or S and Y is a C_{1-3} alkylene group.

2. A compound according to claim 1, wherein said cyclic amine is substituted by a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group.

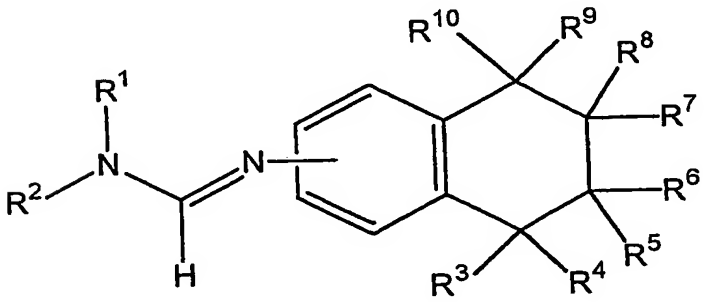
3. A compound according to claim 1 or claim 2 wherein said cyclic amine is fused with a benzene ring.

4. A compound according to claim 3 wherein said benzene ring is substituted by one or two halogen atoms, C_{1-6} alkyl groups or C_{1-6} alkoxy groups.

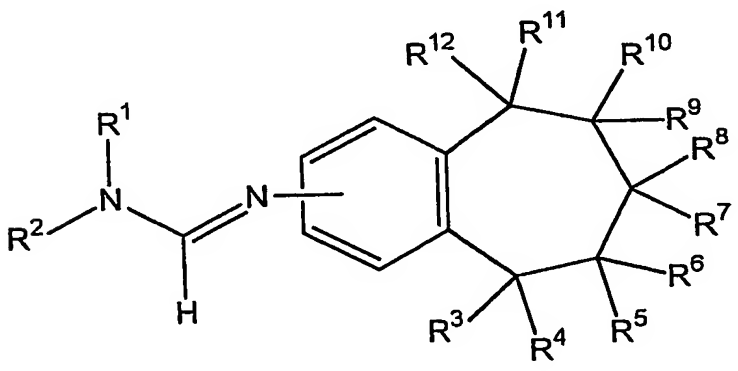
5. A compound according to claim 1 represented by the following formulae (II), (III) and (IV):



(II)



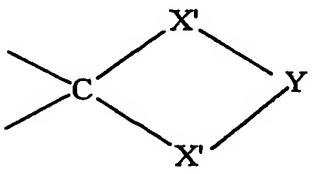
(III)



(IV)

wherein R^1 and R^2 independently are a hydrogen atom, a substituted or unsubstituted straight chain or branched chain C_{1-6} alkyl group or C_{1-6} alkoxy group, a substituted or unsubstituted C_{1-6} cycloalkyl group or a C_{1-6} cycloalkoxy group, or an aralkyl group, or R^1 and R^2 form, together with the nitrogen atom to which they are bonded, a cyclic amine; R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are independently a hydrogen atom or the group $-X-R^{13}$ wherein X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group.

6. A compound according to claim 5 wherein R^3 and R^4, R^5 and R^6, R^7 and R^8, R^9 and R^{10}, and/or R^{11} and R^{12} together with the carbon atom in the ring to which they are both bonded, form a C=O group, a C=S group or the following group:



wherein both of X' are O or S and Y is a C_{1-3} alkylene group.

7. A compound according to claim 5 or claim 6 wherein R^1 and R^2 form together with the nitrogen atom to which they are bonded, a four-membered, five-membered or six-membered cyclic amine.

8. A compound according to claim 7 wherein said six-membered cyclic amine is fused with a benzene ring.

9. A compound according to claim 5 wherein R^1 and R^2 are a C_{1-6} alkyl group.

10. A compound according to any preceding claim which possesses serotonin 5-HT7 receptor antagonist activity and/or muscarinic m4 receptor agonist activity.

11. A compound according to claim 10 which additionally has a low or substantially no dopaminergic D2 receptor affinity.

12. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 11 admixed with a pharmaceutically acceptable carrier.

13. Use of a compound according to any one of claims 1 to 11 for the preparation of a medicament for the treatment or prophylaxis of schizophrenia and/or bipolar disorder.

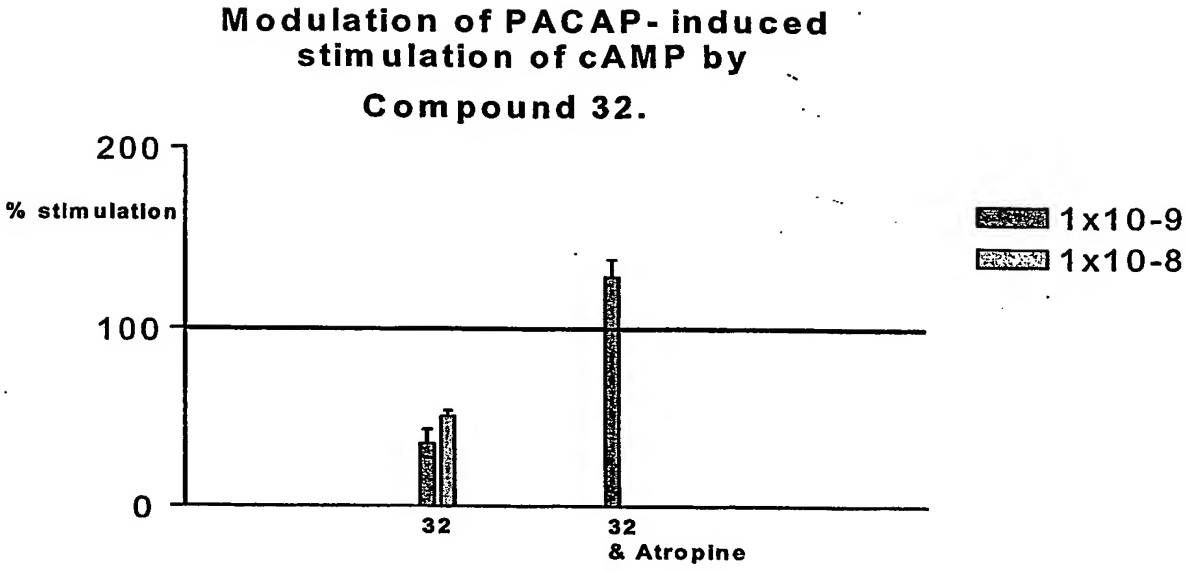

Modulation of PACAP- induced stimulation of cAMP by Compound 32.
200
% stimulation
100
0
32
32
& Atropine
1x10-9
1x10-8

Figure 1